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Comparison of Survival Outcomes Between Patients With Malignant Mixed Mullerian Tumors and High-Grade Endometrioid, Clear Cell, and Papillary Serous Endometrial Cancers

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Abstract

Introduction—Malignant mixed mullerian tumors (MMMTs) are an aggressive subtype of endometrial cancer (EC). Previous studies compare survival between high-grade endometrioid (EM), clear cell (CC), and papillary serous (PS) ECs; yet few studies compare MMMTs to these aggressive subtypes. The goal of this study was to compare recurrence-free survival (RFS), disease-specific survival (DSS), and overall survival (OS) among EC subtypes.

Methods—We conducted a retrospective cohort study of EC cases treated at Magee-Women's Hospital between 1996 and 2008. Kaplan-Meier estimates of RFS, DSS, and OS as well as and log-rank tests were used to compare survival distributions between histologic subtypes. Cox regression was used to estimate hazard ratios for histologic subtypes, adjusted for other significant prognostic factors. Interactions between histologic subtype and prognostic factors were examined to assess effect modification.

Results—This cohort included 81 MMMT (15%), 254 high-grade EM (46%), 73 CC (13%), and 147 PS (26%) cases. Compared to high-grade EM (6%) and CC (7%) cases, relatively more MMMT (12%) and PS (12%) cases were nonwhite. Stage differed significantly among the subtypes, with 36%, 34%, 37%, and 51% of MMMT, high-grade EM, CC, and PS cases, respectively, diagnosed at advanced late stage ($P < 0.001$). Kaplan-Meier curves and log-rank tests showed similar RFS, DSS, and OS between MMMT, high-grade EM, CC, and PS cases stratified by stage. In adjusted Cox regression models, RFS and DSS were not significantly different

between MMMT and other subtypes. High-grade EM cases had a significantly better OS compared to MMMT cases (HR, 0.63; 95% confidence interval [CI], 0.41–0.98).

Conclusions—This is the first retrospective study to suggest that certain survival outcomes are similar among MMMT, high-grade EM, CC, and PS subtypes. Other large-scale studies are needed to confirm these findings.

Keywords

Mortality; Aggressive endometrial cancers; Carcinosarcoma

Malignant mixed müllerian tumors (MMMTs) are an aggressive form of endometrial cancer (EC) with malignant epithelial and stromal components. Although MMMTs comprise less than 5% of ECs, 5-year overall survival (OS) rates for this subtype are extremely low, ranging from 20% to 35%.^{1–7} In comparison, low-grade endometrioid (EM) ECs have a 5-year OS rate approaching 90%.⁸ The significant morbidities associated with the MMMT subtype (ie, local and distant recurrences) represent challenges in the management of this invasive malignancy. Between 33% and 55% of MMMT cases have recurrence within 2 years of diagnosis.^{7,9} Studies that examine the MMMT subtype exclusively report that extent of the tumor, intraperitoneal metastasis, lymph node involvement, age, race, and stage predict recurrence and death.^{7,10–16}

In the 1988 International Federation of Gynecology and Obstetrics (FIGO) staging criteria, MMMTs were grouped as uterine sarcomas owing to the presence of a sarcomatous component and poor survival in comparison to epithelial-derived EC. Consequently, MMMTs were excluded from FIGO staging.¹⁷ Pathologically, several theories of MMMT histogenesis exist; the most commonly accepted hypothesis is that most MMMTs are monoclonal, that is, derived from a single stem cell.¹⁸ The sarcomatous component of the tumor is derived either from the carcinoma during the progression of the tumor or from divergent differentiation of the 2 components from the same stem cell that occurs early in the development of the tumor.¹⁸ Evidence from Silverberg¹⁹ and Nordal¹³ suggests that the malignant epithelial component of MMMTs drives the aggressive behavior of this tumor. Malignant mixed müllerian tumors with a papillary serous (PS) or clear cell (CC) carcinomatous elements had a greater tendency for distant metastasis and poor survival compared to a low-grade EM element. Furthermore, MMMTs tend to metastasize via the lymphatic system, similar to the pattern of spread in epithelial EC subtypes. In contrast, 2 uterine sarcoma subtypes, leiomyosarcomas and endometrial stromal sarcomas, metastasize primarily through the hematogenous route.²⁰ Malignant mixed müllerian tumors share epidemiologic risk factors with EM-type ECs, including increasing weight, estrogen replacement therapy, and nulliparity.^{21,22} Based on this evidence, the most recent revision of the FIGO staging guidelines concluded that MMMTs should be staged as epithelial EC.^{23,24}

Three studies have examined survival differences between MMMT and high-grade EM, CC, and PS EC patients.^{25–27} Similar to MMMTs, these epithelial subtypes are less common and associated with poor outcomes. The purpose of these studies was to discern whether MMMTs should be incorporated into clinical treatment trials with these other high-risk subtypes. Collectively, evidence from these studies suggests that MMMTs have significantly worse OS compared to high-risk epithelial subtypes and should not be included with these subtypes.

Although advanced stage is associated with poor prognosis in MMMTs, shorter OS times have been observed in patients with MMMTs confined to the uterus.^{26,27} In adjusted Cox regression models, MMMTs had worse OS compared to non-EM cases (CC and PS subtypes combined) adjusted for stage²⁷ and worse OS and RFS than high-grade EM cases adjusted

for stage and vascular invasion.²⁵ Although valuable, these studies are limited by small sample sizes and lack of control for important prognostic factors in survival outcomes. Our primary goals were to confirm or challenge the findings from previous studies, assess survival endpoints, and examine possible effect modification between histologic subtype and prognostic factors.

MATERIALS AND METHODS

Study Population

A retrospective cohort of high-risk EC cases (N = 555) was diagnosed and/or treated at Magee-Women's Hospital between 1996 and 2008. Primary treatment included surgical intervention (hysterectomy with or without removal of the fallopian tubes and ovaries) in 88% (n = 491) of cases. Of the 491 cases, lymph node dissection was performed in 354 cases (72%).

Nonsurgical cases (n = 64 [12%]) differed significantly from surgical cases with respect to stage (χ^2 , $P < 0.001$); 50% of nonsurgical cases had late-stage tumors compared to 33% of surgical cases.

Clinical, pathological, and follow-up data were retrieved from the University of Pittsburgh Medical Center (UPMC) Network Cancer Registry using an honest broker. The UPMC Network Cancer Registry gathers demographic, medical history, diagnostic findings, and treatment and outcome information on patients with cancer treated within the network. Endometrial cancer cases with an *International Classification of Diseases for Oncology (ICD-O, 3rd Edition, 2000)* primary site code between C54.0–C54.9 and C55.9 were included in this analysis. Adenosarcomas were not included with MMMTs, as the prognosis for this histology type is considered to be different than MMMTs. Information on age, race, weight, and height at the time of EC diagnosis, history of additional cancer primaries, stage, grade (where applicable), treatment, tumor histology, date of diagnosis, and date of death were collected from electronic medical records. Data registrars collect information on the cause and date of death through periodic follow-up assessments on cases remaining in the UPMC network for health care. For cases that do not continue to receive care in the UPMC Network, registrars contact the primary physician and oncologist of the case to ascertain vital status. As a last assessment of vital status, the Social Security Death Index database was examined twice a year. Tumor histology was determined by a gynecologic pathologist at the time of diagnosis and was abstracted from the pathology report. This study was approved by the University of Pittsburgh Institutional Review Board.

Statistical Analysis

Demographic and clinical characteristics were compared between the histologic subtypes using χ^2 tests for categorical variables and analysis of variance for continuous variables. Nonsurgical cases were excluded from survival analyses. Stage-specific Kaplan-Meier curves were compared using the log-rank test to assess the equality of recurrence-free survival (RFS), disease-specific survival (DSS), and OS between the subtypes. Multivariable Cox proportional hazards modeling was used to estimate the hazard ratios (HRs) for these survival outcomes associated with histologic subtype. Malignant mixed müllerian tumor was the reference histologic subtype. Models were adjusted for age, body mass index (BMI), stage (early stages [I and II] and late stages [III and IV]), postoperative treatment (surgery only; surgery and radiotherapy; surgery and chemotherapy; surgery, radiotherapy, and chemotherapy), and year of diagnosis. Body mass index categories were based on the Centers for Disease Control and Prevention definitions.²⁸ Because the 1988 FIGO staging guidelines for epithelial EC did not apply to MMMTs, stage was retrospectively assigned to

these cases based on the Tumors, Nodes, Metastases classification and pelvic washing information in the pathology report. Five MMT cases and one PS case without stage information were also excluded from the survival analyses.

Recurrence-free survival, DSS, and OS times were defined as the number of days between the date of diagnosis and the date of recurrence, death from EC, or death from any cause, respectively. Only patients known to be disease-free after the primary surgery were included in the RFS analysis ($n = 403$). Patients lost to follow-up were censored on the last date of contact, and those patients alive at the end of follow-up (December 31, 2008) were censored at that time. We examined interactions between histologic subtype and prognostic factors to test the null hypothesis that the effect of prognostic factors on survival was similar among histologic subtypes. Interactions were added to the main effects model one by one and tested with Wald χ^2 tests; interactions significant at the $P < 0.10$ level were retained in the final model. The proportional hazards assumption was assessed for each covariate by the Grambsch and Therneau method.²⁹

RESULTS

Of the identified 1964 EC cases diagnosed at Magee-Women's Hospital between 1996 and 2008, 555 had a diagnosis code pertaining to the 4 histologic subtypes under investigation, including 81 (15%) MMT, 254 (46%) high-grade EM, 73 (13%) CC, and 147 (26%) PS cases. Low-grade EM histology accounted for most of the excluded cases. Distributions of demographic and clinical characteristics are shown by histologic subtype in Table 1. Age, race, and BMI were borderline significantly different between the 4 subtypes. Clear cell and PS cases had a higher mean age (68 and 67 years, respectively) compared to high-grade EM and MMT cases (65 years). Twelve percent of MMT and PS cases were nonwhite compared to 7% of CC and 6% of high-grade EM. Normal BMI was more common among PS (27%) and CC cases (23%) compared to MMT (17%) and high-grade EM cases (15%).

History of additional primary cancers was more common in PS cases (26%) compared to MMT (16%), CC (15%), and high-grade EM (13%) cases. The most common additional cancer primaries were breast, ovarian, and colorectal cancers. Breast cancer prevalence was highest among the MMT and PS cases (14%), and colorectal cancer prevalence was highest among PS cases (5%). Ovarian cancer prevalence was highest among the high-grade EM cases (3%). Stage distributions differed significantly across the subtypes. Fifty-one percent of PS cases were late stage compared to 36% of MMT, 34% of high-grade EM, and 37% of CC cases. Lymph node metastases were most common in the PS cases (23%), followed by CC (14%), high-grade EM (13%), and MMT cases (6%). Type of postoperative treatment differed significantly between the 4 subtypes; surgery plus chemotherapy was relatively more prevalent among the PS cases (35%), followed by CC (29%), MMT (22%), and high-grade EM (12%). Surgery plus radiotherapy was most prevalent among the high-grade EM cases (48%). Combination chemotherapy and radiotherapy use was most prevalent among MMTs (22%) followed by PS (20%), CC (12%), and high-grade EM (7%) cases.

Table 2 shows sites of recurrence by histologic subtype and stage. Across the histologic subtypes, the prevalence of local recurrence ranged between 0% and 2%. Regional and distant recurrences were more common; MMT cases had the highest prevalence of regional recurrence (15%), followed by PS (13%), high-grade EM (10%), and CC (7%). Distant recurrence was most common among high-grade EM (11%), followed by MMT and PS cases (10%), and CC cases (7%).

Stage-specific (stages I and II combined and stages III and IV combined) Kaplan-Meier survival curves for RFS, DSS, and OS are shown in Figures 1–3, respectively. In early- and late-stage cases, RFS and OS were not significantly different among MMMT, high-grade EM, CC, and PS cases ($P > 0.29$). In early-stage cases, DSS was borderline significantly worse for MMMT cases compared to high-grade EM, CC, PS cases ($P = 0.08$). In late-stage cases, DSS was not significantly different among the 4 subtypes ($P = 0.22$).

Multivariable Cox regression models for RFS, DSS, and OS are summarized in Table 3. In the OS model, high-grade EM cases had a significantly better outcome compared to MMMT cases (HR, 0.63; 95% CI, 0.41–0.98). No significant difference in RFS or DSS was observed between the histologic subtypes in the adjusted models. Only late stage was significantly associated with each survival outcome: RFS (HR, 4.27; 95% CI, 2.58–7.06), DSS (HR, 5.16; 95% CI, 2.98–8.93), and OS (HR, 3.32; 95% CI, 2.35–4.69). For DSS and OS, increasing age was significantly associated with increased risk of death. Treatment with radiotherapy and/or chemotherapy significantly reduced the hazard of all-cause mortality compared to surgery alone (HR for combination chemotherapy and radiotherapy, 0.30; 95% CI, 0.15–0.58). No significant interactions between histologic subtype and any prognostic factor were observed for RFS, DSS, or OS.

DISCUSSION

Although increased risk of recurrence and mortality is associated with high-risk EC subtypes, few studies compare the MMMT subtype to high-grade EM, CC, and PS ECs in large cohorts of cases. Here, we report that patients with MMMT had similar RFS and DSS compared to high-grade EM, CC, and PS cases adjusted for age, BMI, stage, postoperative treatment, and year of diagnosis. However, we did observe a significant difference in OS between MMMT and high-grade EM cases. Our findings agree with studies reporting differences between MMMT and high-grade EM cases^{15,22} and conflict with those showing differences between MMMT, CC, and PS cases.^{25–27} A study using the Surveillance, Epidemiology, and End Results database examined approximately 9000 cases, and reported high-grade EM cases had significantly better OS than MMMT cases in a model adjusted for age, race, lymph node dissection, stage, and postoperative radiotherapy.¹⁵ Similarly, Bland et al²² reported that MMMT patients had a significantly shorter progression-free survival interval (23 vs 57 months, $P < 0.001$) and OS (55 vs 92 months, $P < 0.001$) compared to high-grade EM patients.

Other studies have also demonstrated survival differences between high-grade EM and MMMT cases; however, these studies also report differences among MMMT, CC, and PS cases. George et al²⁵ compared MMMT cases ($n = 32$) to high-grade EM ($n = 41$), CC ($n = 14$), and PS ($n = 11$) cases and reported time to death and recurrence were significantly shorter in MMMT cases compared to high-grade EM, CC, and PS cases. Likewise, Amant et al²⁶ reported that MMMTs ($n = 33$) had a shorter OS compared to non-EM (CC and PS; $n = 54$) and high-grade EM ($n = 50$) cases. Poor survival in MMMT cases remained statistically significant after adjustment for FIGO stage. In a case-control study of 45 MMMT cases and 45 high-grade EM, CC, and PS cases, median OS was twice as long in the heterogeneous EC group compared to MMMTs.

Previously, MMMTs were classified as a uterine sarcoma subtype owing to the presence of a sarcomatous component, invasive tumor spread, and poor survival in comparison to purely epithelial EC. Recent clinical data have prompted reconsideration of this notion. Factors related to excess estrogen exposure such as obesity, nulliparity, and estrogen replacement therapy are common features of both MMMT and high-grade EM cases.^{21,30} In our study, the distributions of BMI were similar for MMMTs and high-grade EMs; 48% of MMMT

and high-grade EM cases were obese. Moreover, the propensity for lymphatic spread is a unifying characteristic between MMMT and high-risk EC.²⁰ While only 6% of MMMT cases in this study had positive lymph node involvement, compared to 13% of high-grade EM cases, 14% of CC cases, and 23% of PS cases, a large proportion of MMMT cases did not have a lymph node examination. Lack of a lymph node examination may have contributed to the low prevalence of positive lymph node involvement in this subgroup. Taken together, previous studies in addition to this investigation seem to suggest that MMMTs share risk factors, patterns of disease spread, and histogenesis with high-grade EM, CC, and PS patients. Our study is unique in that we found a significant difference in OS between MMMT and high-grade EM patients but not between MMMT, CC, and PS cases.

We observed an interesting racial disparity with respect to MMMTs. Although race was not significantly different between the subtypes at the traditional α level of 0.05, non-white race was twice as prevalent in the MMMT cases (12%) compared to the high-grade EM (6%) cases. Most nonwhites in our cohort were African American. The incidence of EC subtypes is known to vary by race.³¹ Our finding confirms previous studies, which reported that MMMTs were more common than high-grade EM in nonwhite women.^{15,21,22} Future studies should examine the determinants of aggressive EC subtypes in nonwhite women.

Surgery is the primary treatment for all ECs and is curative in most low-risk cancers. Postsurgical treatments for MMMTs have included radiotherapy,^{32–34} paclitaxel,³⁵ cisplatin,³⁶ and combination chemotherapy and radiotherapy.^{37,38} These studies demonstrated significant improvements in both OS and RFS associated with treatment. Three phase III randomized clinical trials (RCTs) have examined treatment in patients with MMMTs. Two RCTs compared the efficacy of ifosfamide as a single agent versus ifosfamide in combination with paclitaxel³⁵ or cisplatin.³⁶ A meta-analysis of these 2 trials showed improved OS and progression free survival (PFS) in women who received combination therapy versus ifosfamide alone.³⁹ The third RCT examined the efficacy of whole abdominal irradiation versus cisplatin-ifosfamide and mesna and reported no significant difference in OS or PFS for patients receiving whole abdominal irradiation versus cisplatin-ifosfamide and mesna. In our study, 22% of MMMTs were treated with combination radiotherapy and chemotherapy. Combination therapy was associated with a reduced risk of all-cause mortality. Although our data did not permit examination of specific chemotherapy agents, we hope to address this question in future investigations.

The major strengths of this study include reliable data from a reputable cancer registry, a large sample size of high-risk subtypes with numerous events, and adjustment for other prognostic factors. In other case series that have examined outcomes in these high-risk subtypes, sample sizes have ranged from 90 to 137 cases. In our cohort of 486 cases, we were able to test the independent effect of histologic subtype on survival outcomes while adjusting for other prognostic factors. Furthermore, we were able to test interactions between histologic subtype and prognostic factors to evaluate potential effect modification. Potential limitations of this study include the retrospective study design and lack of generalizability to nonsurgical EC cases due to our inclusion of surgical cases in this analysis.

In conclusion, we found evidence that RFS, DSS, and OS were similar for patients with MMMT, CC, and PS ECs. Owing to the low incidence and high mortality associated with these subtypes, efforts to enroll sufficient numbers of patients into clinical trials should be undertaken to explore optimal treatment protocols. Participation from multiple institutions and long accrual periods will be required to meet this goal. Our data suggest that MMMT cases resemble other high-risk subtypes and could therefore be included in trials with other high-risk epithelial cancers. A large number of cases within each histologic subtype should

be recruited to allow for meaningful subgroup analyses. Future explorations of the MMMT subtype should examine survival differences with respect to the type of epithelial component that arises with the malignant stromal component. Previous studies suggest that the epithelial component drives the aggressive behavior of these tumors^{19,40,41}; however, little evidence is available to predict which epithelial subtypes have worse survival. In addition, future studies should explore the molecular biology of MMMTs. This would not only increase our understanding of the carcinogenesis of these tumors but also help to identify potential molecule-targeted treatments that can be used for treatment.

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References

1. Callister M, Ramondetta LM, Jhingran A, et al. Malignant mixed Mullerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. *Int J Radiat Oncol Biol Phys*. 2004; 58:786–796. [PubMed: 14967435]
2. Dinh TV, Slavin RE, Bhagavan BS, et al. Mixed mullerian tumors of the uterus: a clinicopathologic study. *Obstet Gynecol*. 1989; 74:388–392. [PubMed: 2548134]
3. Schweizer W, Demopoulos R, Beller U, et al. Prognostic factors for malignant mixed mullerian tumors of the uterus. *Int J Gynecol Pathol*. 1990; 9:129–136. [PubMed: 2158940]
4. Spanos WJ Jr, Peters LJ, Oswald MJ. Patterns of recurrence in malignant mixed mullerian tumor of the uterus. *Cancer*. 1986; 57:155–159. [PubMed: 3000571]
5. Podczaski ES, Woomert CA, Stevens CW Jr, et al. Management of malignant, mixed mesodermal tumors of the uterus. *Gynecol Oncol*. 1989; 32:240–244. [PubMed: 2536000]
6. Nielsen SN, Podratz KC, Scheithauer BW, et al. Clinicopathologic analysis of uterine malignant mixed mullerian tumors. *Gynecol Oncol*. 1989; 34:372–378. [PubMed: 2548936]
7. Yamada SD, Burger RA, Brewster WR, et al. Pathologic variables and adjuvant therapy as predictors of recurrence and survival for patients with surgically evaluated carcinosarcoma of the uterus. *Cancer*. 2000; 88:2782–2786. [PubMed: 10870061]
8. Sonoda Y, Barakat RR. Screening and the prevention of gynecologic cancer: endometrial cancer. *Best Pract Res Clin Obstet Gynaecol*. 2006; 20:363–377. [PubMed: 16364689]
9. Wong L, See HT, Khoo-Tan HS, et al. Combined adjuvant cisplatin and ifosfamide chemotherapy and radiotherapy for malignant mixed mullerian tumors of the uterus. *Int J Gynecol Cancer*. 2006; 16:1364–1369. [PubMed: 16803531]
10. Garg G, Shah JP, Kumar S, et al. Ovarian and uterine carcinosarcomas: a comparative analysis of prognostic variables and survival outcomes. *Int J Gynecol Cancer*. 2010; 20:888–894. [PubMed: 20606539]
11. Wu TI, Hsu KH, Huang HJ, et al. Prognostic factors and adjuvant therapy in uterine carcinosarcoma. *Eur J Gynaecol Oncol*. 2008; 29:483–488. [PubMed: 19051818]
12. Iwasa Y, Haga H, Konishi I, et al. Prognostic factors in uterine carcinosarcoma: a clinicopathologic study of 25 patients. *Cancer*. 1998; 82:512–519. [PubMed: 9452269]
13. Nordal RR, Kristensen GB, Stenwig AE, et al. An evaluation of prognostic factors in uterine carcinosarcoma. *Gynecol Oncol*. 1997; 67:316–321. [PubMed: 9441781]
14. Sartori E, Bazzurini L, Gadducci A, et al. Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. *Gynecol Oncol*. 1997; 67:70–75. [PubMed: 9345359]
15. Bansal N, Herzog TJ, Seshan VE, et al. Uterine carcinosarcomas and grade 3 endometrioid cancers: evidence for distinct tumor behavior. *Obstet Gynecol*. 2008; 112:64–70. [PubMed: 18591309]

16. Galaal K, Kew FM, Tam KF, et al. Evaluation of prognostic factors and treatment outcomes in uterine carcinosarcoma. *Eur J Obstet Gynecol Reprod Biol.* 2009; 143:88–92. [PubMed: 19201517]
17. Pecorelli S, Benedet JL, Creasman WT, et al. FIGO staging of gynecologic cancer. 1994–1997 FIGO Committee on Gynecologic Oncology. International Federation of Gynecology and Obstetrics. *Int J Gynaecol Obstet.* 1999; 65:243–249. [PubMed: 10428343]
18. McCluggage WG. Malignant biphasic uterine tumours: carcinosarcomas or metaplastic carcinomas? *J Clin Pathol.* 2002; 55:321–325. [PubMed: 11986333]
19. Silverberg SG, Major FJ, Blessing JA, et al. Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases. *Int J Gynecol Pathol.* 1990; 9:1–19. [PubMed: 2152890]
20. McCluggage WG. Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. *Int J Gynecol Cancer.* 2002; 12:687–690. [PubMed: 12445244]
21. Zelmanowicz A, Hildesheim A, Sherman ME, et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors. *Gynecol Oncol.* 1998; 69:253–257. [PubMed: 9648597]
22. Bland AE, Stone R, Heuser C, et al. A clinical and biological comparison between malignant mixed mullerian tumors and grade 3 endometrioid endometrial carcinomas. *Int J Gynecol Cancer.* 2009; 19:261–265. [PubMed: 19396006]
23. D'Angelo E, Prat J. Uterine sarcomas: a review. *Gynecol Oncol.* 2010; 116:131–139. [PubMed: 19853898]
24. Prat J. FIGO staging for uterine sarcomas. *Int J Gynaecol Obstet.* 2009; 104:177–178. [PubMed: 19135669]
25. George E, Lillemoe TJ, Twiggs LB, et al. Malignant mixed mullerian tumor versus high-grade endometrial carcinoma and aggressive variants of endometrial carcinoma: a comparative analysis of survival. *Int J Gynecol Pathol.* 1995; 14:39–44. [PubMed: 7883424]

FIGURE 1.

Recurrence-free survival of early-stage (A) and late-stage (B) MMTT, high-grade EM, CC, and PS.

FIGURE 2.

Disease-specific survival of early-stage (A) and late-stage (B) MMT, high-grade EM, CC, and PS.

FIGURE 3.
Overall survival of early-stage (A) and late-stage (B) MMT, high-grade EM, CC, and PS.

TABLE 1

Demographic and clinical characteristics by EC subtype (N = 555)

	MMMT (n = 81)	High-Grade EM (n = 254)	Clear Cell (n = 73)	Papillary Serous (n = 147)	P (df)
Age, Mean (SD)	65 (10)	65 (12)	68 (11)	67 (12)	0.06 (3)
Race					
White	71 (88%)	239 (94%)	68 (93%)	129 (88%)	0.09 (3)
Nonwhite	10 (12%)	15 (6%)	5 (7%)	18 (12%)	
Body Mass Index					
Normal (BMI <25 kg/m ²)	14 (17%)	39 (15%)	17 (23%)	40 (27%)	0.08 (9)
Overweight (BMI 25–30 kg/m ²)	22 (27%)	72 (28%)	23 (31%)	35 (24%)	
Obese (BMI >30 kg/m ²)	39 (48%)	121 (48%)	32 (44%)	57 (39%)	
Unknown	6 (7%)	22 (9%)	1 (1%)	15 (10%)	
Additional Cancer Primaryes [*]					
No	66 (81%)	214 (84%)	62 (85%)	106 (72%)	0.05 (6)
Yes	13 (16%)	34 (13%)	11 (15%)	38 (26%)	
Breast	11 (14%)	15 (6%)	7 (10%)	20 (14%)	
Ovarian	0 (0%)	6 (3%)	0 (0%)	2 (1%)	
Colorectal	1 (1%)	2 (1%)	1 (1%)	8 (5%)	
Other	1 (1%)	11 (4%)	3 (4%)	8 (5%)	
Unknown	2 (2%)	6 (2%)	0 (0%)	3 (2%)	
Stage [†]					
Early (I and II)	47 (58%)	167 (66%)	46 (63%)	70 (48%)	<0.001 (6)
Late (III and IV)	29 (36%)	87 (34%)	27 (37%)	76 (51%)	
Unknown	5 (6%)	0 (0%)	0 (0%)	1 (1%)	
Lymph Node Involvement					
Negative	35 (43%)	124 (49%)	39 (53%)	68 (46%)	0.009 (9)
Positive	5 (6%)	32 (13%)	10 (14%)	34 (23%)	
No nodes examined	35 (43%)	89 (35%)	23 (32%)	38 (26%)	
Unknown	6 (8%)	9 (3%)	1 (1%)	7 (5%)	
Postoperative Therapy					
No surgery	7 (9%)	37 (16%)	8 (11%)	12 (8%)	<0.001 (12)

	MMMT (n = 81)	High-Grade EM (n = 254)	Clear Cell (n = 73)	Papillary Serous (n = 147)	P (df)
Surgery only	15 (19%)	47 (18%)	9 (12%)	27 (18%)	
Surgery + CT	18 (22%)	31 (12%)	21 (29%)	52 (35%)	
Surgery + RT	23 (28%)	122 (48%)	26 (36%)	27 (18%)	
Surgery + CT + RT	18 (22%)	17 (7%)	9 (12%)	29 (20%)	

² Pvalue for categorical variables; analysis of variance Pvalue for continuous variables.

^{*} Breast, ovarian, and colorectal cancers were the most common additional cancer primaries.

[†] Stage was assigned retrospectively to MMMT cases.

CT, Chemotherapy; RT, radiotherapy.

TABLE 2

Site of recurrence among disease-free cases overall and by stage for each histologic subtype

Recurrences = 92 N = 403*	MMMT (n = 54)	High-Grade EM (n = 186)	Clear Cell (n = 55)	Papillary Serous (n = 108)
No Known Recurrence	40 (74%)	142 (76%)	46 (83%)	83 (77%)
Early stage (I and II)	34 (63%)	114 (61%)	37 (67%)	52 (48%)
Late stage (III and IV)	6 (11%)	28 (15%)	9 (16%)	31 (29%)
Local Recurrence	1 (2%)	2 (1%)	1 (2%)	0 (0%)
Early stage (I and II)	1 (2%)	1 (0.5%)	1 (2%)	0 (0%)
Late stage (III and IV)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Regional Recurrence	8 (15%)	20 (10%)	4 (7%)	14 (13%)
Early stage (I and II)	2 (4%)	8 (4%)	3 (5%)	3 (3%)
Late stage (III and IV)	6 (11%)	12 (6%)	1 (2%)	11 (10%)
Distant Recurrence	5 (10%)	20 (11%)	4 (7%)	11 (10%)
Early stage (I and II)	3 (6%)	14 (8%)	0 (0%)	3 (3%)
Late stage (III and IV)	2 (4%)	6 (3%)	4 (7%)	8 (7%)
Disease Has Recurred but Unknown Type	0 (0%)	2 (1%)	0 (0%)	0 (0%)
Early stage (I and II)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Late stage (III and IV)	0 (0%)	2 (1%)	0 (0%)	0 (0%)

Regional recurrence: Adjacent tissue or organ and/or regional lymph nodes. Distant recurrence: Lung, liver, bone, multiple sites.

* Disease-free cases.

TABLE 3

Cox regression models for RFS, DSS, and OS

Variable	RFS* (N = 403, Recurrences = 92)			DSS (N = 486, Deaths = 76)			OS (N = 486, Deaths = 181)		
	Multivariable [†]	P [‡] (df)		Multivariable [†]	P [‡] (df)		Multivariable [†]	P [‡] (df)	
Histology Type									
MMMT	1.00	0.54 (3)		1.00	0.11 (3)		1.00	0.21 (3)	
High-grade EM	0.67 (0.35, 1.28)			0.48 (0.24, 0.95)			0.63 (0.41, 0.98)		
Clear cell	0.64 (0.27, 1.51)			0.46 (0.19, 1.14)			0.64 (0.37, 1.12)		
Papillary serous	0.62 (0.32, 1.22)			0.78 (0.39, 1.55)			0.67 (0.41, 1.08)		
Age, yrs	1.02 (0.99, 1.04)	0.09		1.02 (1.00, 1.05)	0.02		1.03 (1.02, 1.05)	<0.001	
Body Mass Index									
Normal weight	1.00	0.15 (3)		1.00	0.26 (3)		1.00	0.10 (3)	
Overweight	0.66 (0.37, 1.18)			0.58 (0.30, 1.11)			0.69 (0.45, 0.98)		
Obese	0.69 (0.40, 1.21)			0.87 (0.48, 1.56)			1.06 (0.72, 1.56)		
Unknown	0.21 (0.05, 0.93)			0.37 (0.08, 1.68)			0.60 (0.26, 1.37)		
Stage									
Early (I and II)	1.00	<0.001		1.00	<0.001		1.00	<0.001	
Late (III and IV)	4.27 (2.58, 7.06)			5.16 (2.98, 8.93)			3.32 (2.35, 4.69)		
Postoperative Therapy									
Surgery only	1.00	0.59 (3)		1.00	0.19 (3)		1.00	0.001 (3)	
Surgery + CT	0.88 (0.44, 1.76)			0.64 (0.33, 1.26)			0.58 (0.37, 0.91)		
Surgery + RT	0.84 (0.44, 1.60)			0.72 (0.36, 1.44)			0.55 (0.36, 0.83)		
Surgery + CT + RT	0.58 (0.25, 1.32)			0.33 (0.12, 0.90)			0.30 (0.15, 0.58)		

* Disease-free cases included in RFS analysis.

[†]Year of diagnosis included.[‡]Wald Pvalue.

df, degrees of freedom for multiparameter tests.